Alliance
PHARMACEUTICAL CORP.

January 24, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. 2004D-0462; "Draft Guidance for Industry: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes"

Dear Sir/Madam,

We respectfully submit the attached comments on the draft guidance entitled "Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes" for your review and consideration.

If you have further questions regarding these comments, please contact me at (858) 410 5326 or via email at djr@allp.com

Sincerely,

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Comments to "Guidance for Industry: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes"

General Comments:

FDA has done a good job in addressing problems of development, safety and efficacy of Oxygen Therapeutics. A lot of detail has been provided that will be most helpful for companies that are early in their development efforts. However, because this document is so specific in many instances, it is more important that FDA clearly defines what products are being referred to, as many items may be only relevant to one particular class of oxygen therapeutic (i.e., Hb solutions versus PFC emulsions). We would suggest that the document is split into two parts, one for comments and recommendations on safety and efficacy for PFCs and the other for Hb based products.

There are many cases where the FDA refers to 'evidence' without providing any references from peer-reviewed literature. FDA usually requires sponsors to cite relevant literature. Hence, it would be very helpful if specific claims in this Guidance Document about 'known' side effects or 'evidence' of unwanted characteristics of either Hb or PFC-based oxygen carriers were referenced with published literature that is available to the scientific community.

Specific Comments and Questions

Section III, A. General; line 1. We would suggest that the document refers to Perfluorochemicals (PFCs) throughout – Fluorochemical and perfluorochemical are used in the document.

Section III, A. General; last line. We suggest deleting "high concentrations of inspired oxygen" and replace with "depending on the ambient PO2 to which they are exposed".

Section III, B. Safety Considerations; line 1. We recommend changing "…largely unresolved safety-related problems…" to "…incompletely understood safety-related issues…." as this more fairly describes the current status of the field, and it is not yet known whether all of these are real 'problems' or just issues that need further study to elucidate mechanisms.

Section III, B. Safety Considerations; Section entitled "Toxicities known or thought to be associated with one or more of the current perfluorochemical emulsions ……"

=> 1. Thrombocytopenia. Line 3. We suggest replace "compounds" with "emulsions"

=> 4. "Flu-like" Symptoms. The last sentence in this section stating that the " …etiology of this phenomenon in not known…" is not accurate, and does not do justice to the work that has been done to understand this biological effect. On the

contrary, many studies have been done and some have been published to elucidate this mechanism, which involves opsonization by plasma proteins followed by macrophage (and perhaps monocyte) mediated phagocytic clearance of the emulsion particles from the circulation. The severity of phenomenon appears to be related to the size of the particles.

Section III, C. Efficacy Considerations; 2. Perioperative Indication. The purpose or implied message of the last (second) paragraph in this section is unclear. Is this intended to suggest that a sponsor will be required by FDA to run additional trials in unstable or trauma patients, even if a company pursues a purely "elective surgery" indication in a specific surgical patient population, and the product label clearly indicates that the product has NOT been evaluated in critically ill or unstable patients or in trauma? This should be clarified in the Guidance Document, and it would be helpful for FDA to provide some specific guidance as to how much additional clinical data would suffice, e.g., a supportive Phase 2 study, as opposed to a large Phase 3 trial.

Section III, C. Efficacy Considerations; 3. Trauma. The latter half of the first paragraph on Page 9 suggests that a 'noninferiority' claim for an oxygen therapeutic compared to blood transfusion might not qualify for running the trial under the exception of informed consent. However, FDA should clarify whether a noninferiority claim could be used for approval of an oxygen therapeutic that was compared against transfusion of blood in an appropriately designed trial that was performed with full informed consent?

Section IV, A. Preclinical Evaluation; 1. Characterization of the Product. This section is confusing, as it does not specify whether the list of proposed characterizations is for Hb or PFC-based products. In fact, the majority of the items a. through j. are only relevant for Hb-based products. It would be easier to interpret if two lists were provided, each specific to either Hb or PFC-based products.

Section IV, B. Clinical Evaluation; 1. General, 5th paragraph. This section indicates that FDA is "recommending" clinical studies that include safety and efficacy in both trauma and elective surgery. While this may be desirable, it may be too expensive and time consuming for a company that is only seeking a specific surgical indication. Hence, FDA should provide some guidance as to whether it is possible to potentially get an approval without having parallel trauma studies, provided that the safety profile is excellent and that the risk-benefit is clearly in favor of using the product for the indication that was studied.

Section IV, B. Clinical Evaluation; 2. Elective Surgery, 2nd paragraph. The recommendation by FDA to "…conduct concentration/dose toxicity trials to determine the maximum tolerated dose of an oxygen therapeutic…" is troublesome, as this is generally done in preclinical GLP toxicology studies in a variety of animal species. Most IRB or Ethics Committees would probably not approve a study in which the intent is to escalate dosing until acute drug-dependent toxicity is documented. The appropriate dose of a drug that can be shown to be efficacious in Phase 3, should be selected based on having an adequate safety margin below the toxic doses that have been established/demonstrated in preclinical toxicology studies. Also, the reference to use

"…non-linear mixed-effects modeling…" is something that will be unfamiliar to most readers, and an appropriate reference should be provided.

Section IV, B. Clinical Evaluation; 2. Elective Surgery; End of 2nd paragraph. It is stated that a suitable trial design might include the enrollment of patients requiring 2 or more units of red blood cells. It is requested that clarification is given on the word "confirm". While it is possible to enroll a group of patients that historically might need the required number units, it will be impossible to ensure that all patients enrolled require or receive the specified number of units. FDA's guidance on this point is requested.

Section IV, B. Clinical Evaluation; 2. Elective Surgery; 4th paragraph. It would be helpful to provide more specific statistical guidance as to what FDA means when they say that they "…are willing to accept a modest level of uncertainty…." when comparing safety equivalency between an oxygen therapeutic and red blood cells.